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Evaluation of metabolic parameters of microsatellites stable and instable colorectal cancer patients via PET/CT

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ABSTRACT

Aims: Microsatellite instability has been determined as an important indicator in selecting chemotherapy drugs in colorectal cancer. Within the scope of this research, we aimed to elucidate the pathology reports and determine whether the metabolic parameters detected by PET/CT differ in MSI-positive and negative patients.

Methods: A total of 35 patients were analyzed retrospectively. The patient population consisted of patients who applied to the Nuclear Medicine Department with a diagnosis of colon or rectum cancer, underwent PET/CT imaging for staging purposes, and were operated on.

Results: A total of 35 colon or rectum cancer patients were included in this retrospective analysis. When microsatellite instability was analyzed among the patients, it was found that female patients comprised 4 microsatellite instability-positive and 16 microsatellite instability-negative individuals. On the other hand, 5 of the males were microsatellite instability positive, and 10 were microsatellite instability negative. The mean SUVmax value was 16.4±8.2, SUVmean was 8.1±1.9, TLG was 392.4±520.8, and MTV was 26.5±25.4 in the microsatellite instability-positive individuals. On the other hand, the mean SUVmax value was 22.7±9.7, SUVmean was 5.2±2.2, TLG was 316.4±325.7, and MTV was 21.7±21.7 in the microsatellite instability-negative individuals.

Conclusion: With the advancement of image analysis technology, MTV, and TLG, volumetric indexes derived from 18F-FDG PET have been proposed for risk stratification of cancer patients. Regarding the outcomes of this research, the semiquantitative and metabolic parameters obtained by PET/CT are not different in colorectal cancer cases with instable and stable microsatellites.

Keywords: Colorectal cancer, microsatellite instability, positron emission tomography/computed tomography (PET/CT), mismatch repair genes (MMR), standardized uptake value (SUV)

INTRODUCTION

Colon Cancer is the third most common type of cancer among women and men worldwide. The average 5-year survival rate for colon cancer is 63%, and this rate is 90% in the early stage, 71% in the locally advanced stage, and 14% in the metastatic stage. In the current staging of colon cancer, Tumor size and depth, number of metastatic lymph nodes (LN), and the presence of distant organ metastases are used. The development of colorectal cancer (CRC) is thought to occur through 2 different mutational pathways called chromosomal instability or microsatellite instability.[1] Chromosomal instability is a common feature in 85% of colorectal cancers. The fact that it can be observed even in the smallest adenoma suggests that chromosomal instability occurs in the very early stages of colorectal cancer development. The microsatellite instability (MSI) pathway effectively develops 15-20% of colorectal cancers.[2] MSI is mainly caused by mutational inactivation of one of the four major mismatch repair (MMR) genes (MSH2, MLH1, MSH6, or PMS2).

Colon cancers with MSI features have different clinical and pathological features than microsatellite-stable ones. MSI has been defined as a positive prognostic factor in colorectal cancers. Tumors with high microsatellite instability (MSI-H) have less possibility of metastasis. It has been suggested that they have a better prognosis.[3]

MSI has been determined as an important indicator in selecting chemotherapy drugs in CRC.[4] Recent studies have shown that CRCs with MSI resist 5-fluorouracil (5-FU) chemotherapy and do not benefit from it.[5] MSI status is evaluated in the pathological sample after invasive

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surgery or biopsy. Therefore, noninvasive methods are needed to evaluate MSI status preoperatively and facilitate immunotherapy of CRC patients.[6]

The 2-[18F]fluoro-2-deoxy-Dglucose (FDG), a glucose analog, is used in Positron Emission Tomography/Computed Tomography (PET/CT). The combined use of PET and CT provides information about the tumor's anatomical and metabolic characteristics, thus enabling more precise staging. It is a noninvasive imaging method that allows diagnosis, staging, and prognosis determination with the metabolic parameters obtained during the study. Morphological changes in colorectal cancers have not yet been determined. The superiority of PET/CT over other radiological methods is that it can show the metabolic/functional changes in the tumor tissue in the early stages when it is not formed.[7] FDG PET/CT has proven useful in diagnosing, staging, detecting recurrence, and evaluating treatment response in CRCs. Response evaluation with PET/CT is performed by visual and/or semiquantitative standardized uptake value (SUV) measurement of glucose metabolism in addition to morphological imaging. It has an important place in determining prognosis.[8]

Previous studies compared metabolic parameters detected by PET/CT in patients with positive and negative MSI. Song et al.[9] found that MSI-H CRCs had higher Metabolic tumor volume (MTV), were younger than MSS types, and were mostly located in the right semicolon. Zhang et al.[10] stated that metabolic parameters obtained from 18F-FDG PET/CT can preoperatively predict the MSI status in CRC and show the best correlation with MTV50%. Li et al.[11] established the 18F-FDG PET/CT radionics prediction model, a noninvasive and objective mechanism for preoperatively diagnosing MSI status in patients with CRC.

Within the scope of this research, we aimed to elucidate the pathology reports and determine whether the metabolic parameters detected by PET/CT differ in MSI-positive and negative patients.

METHODS

A total of 35 patients were analyzed retrospectively. The patient population consisted of patients who applied to the Nuclear Medicine Department with a diagnosis of colon or rectum cancer, underwent PET/CT imaging for staging purposes, and were operated on. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from Dicle Universty Medical Faculty Ethics Committee for Nonınterventional Studies (Date: 20.12.2023, Decision No: 10).

Patients were required to fast for at least 6 h and have a blood glucose level of 140 mg/dL for the FDG PET/CT imaging. FDG at a dose of 0.1 mCI/kg was injected intravenously into the patients. After the injection, the patients were kept in a special lead-coated room for 1 hour for the medication to spread through the whole body, and a CT scan of the whole body (from vertex to knees) was performed. Subsequently, whole-body emission scanning was performed with PET. A 2016 model Siemens Horizon brand PET/CT device with 3D-TOF was used for imaging. The slice thickness of the device was 3 mm, and the images were created according to PET iterative and by the CT bp-LOR reconstruction processing method. The low-dose CT device used for anatomical detail and attenuation correction was adjusted to 80 mA and 120 kV (Siemens Healthcare, GmbH Henkestrasse 127, 91052 Erlangen, Germany). An ROI has been determined from the primary tumor location, and the SUVmax,SUVmean, MTV, and TLG have been calculated.

Pathological evaluation was made by immunohistochemical method. It was evaluated whether there was loss of expression. Preservation of expression was considered normal, and the presence of loss of expression was considered damage.

The MSS and MSI-positive cases were recorded regarding their pathology reports. A senior pathologist evaluated of resected specimens with Immuno-histochemical staining. Specifically, the general pathological types, differentiation grade, TNM stages, and the expression of MMR proteins (MLH1, PMS2, MSH2, and MSH6) were assessed.

Inclusion Criteria

Patients who applied to our institution with a diagnosis of colon or rectum cancer underwent PET/CT imaging for staging.

Exclusion Criteria

Patients with relapses who were previously operated on and individuals with another malignity.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 26.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data and mean and standard deviation for continuous data were given as descriptive values. For comparisons between groups, the "Kolmogorov Smirnov test" was used for two groups, and the "Pearson Chi-Square Test" was used to compare categorical variables. Student's t-test was utilized to compare SUV and other metabolic values of lesions. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

A total of 35 colon or rectum cancer patients were included in this retrospective analysis. The mean age of the patients was 56.2±13.4 years. Of the individuals, 57% (n=20) were female and 43% (n=15) were male. Microsatellite instability was detected in 9 patients, and in 26 patients, microsatellite instability was negative. The pathologic diagnosis was adenocarcinoma in 91% (n=32) of the individuals, while mucinous adenocarcinoma was observed in 9% (n=3). The baseline demographic characteristics of the study group are elaborated in Table 1.

Table 1. The baseline demographic characteristics of the study group

Age	56.2±13.4
Gender (Female/Male)	20/15
Microsatellite instability positive	9
Microsatellite instability negative	26
Pathologic diagnosis	Adenocarcinoma (n=32) Mucinous adenocarcinoma (n=3)

When microsatellite instability was analyzed among the patients, it was found that female patients comprised 4 microsatellite instability-positive and 16 microsatellite instability-negative individuals. On the other hand, 5 of the males were microsatellite instability positive, and 10 were microsatellite instability negative (Table 2).

The mean age of the microsatellite instability-positive patients was 64.2±12.4 years, and microsatellite instability-negative patients were 53.4±12.8 years (Table 2).

Table 2. Comparison of age, gender and metabolic parameters obtained from PET-CT imaging between microsatellite instability positive and negative groups

	Microsatellite instability positive (n=9)	Microsatellite instability negative (n=26)	P-Value
Gender (Female/Male)	4/5	16/10	p>0.05
Age (Year)	64.2±12.4	53.4±12.8	p>0.05
SUVmax	16.4±8.2	22.7±9.7	p>0.05
SUVmean	8.1±1.9	5.2±2.2	p>0.05
TLG	392.4±520.8	316.4±325.7	p>0.05
MTV	26.5±25.4	21.7±21.7	p>0.05

The mean SUVmax value was 16.4±8.2, SUVmean was 8.1±1.9, TLG was 392.4±520.8, and MTV was 26.5±25.4 in the microsatellite instability-positive individuals. On the other hand, the mean SUVmax value was 22.7±9.7, SUVmean was 5.2±2.2, TLG was 316.4± 325.7, and MTV was 21.7±21.7 in the microsatellite instability-negative individuals.

DISCUSSION

Microsatellites are repetitive DNA motifs closely associated with many important genes within the genome. These repetitive sequences consist of 1–6 nucleotides. Each microsatellite consists of two parts: a central core and peripheral flanks. The specificity of the microsatellite depends on the change in the number of repetitive units in the central nucleus. Microsatellites are much more distributed in the non-coding regions of genes. In addition, microsatellites are thought to play an important role in forming and rearranging chromosomal structures that may affect gene replication and expression.[12] Due to mutations or epigenetic changes in DNA mismatch repair (MMR) genes, the normal function of the DNA-MMR system is disrupted, and the number of microsatellite base pairs undergoes a change known as microsatellite instability (MSI). The normal tissue DNA repair system can correct DNA replication errors. However, the possibility of gene mutation increases due to the absence of MMR genes in tumor cells or errors in the replication repair process. MSI can be defined as a change in microsatellite length resulting from inserting or deleting a repeating unit, leading to new microsatellite alleles.[13]

According to the number of mutations of microsatellite regions, three different subtypes are formed: high levels of MSI (MSI-H), low levels of MSI (MSI-L), and stable microsatellite (MSS). Studies have shown that MSI plays an important role in the pathogenesis of malignant tumors and is closely related to the formation and prognosis of many malignancies. Most studies have revealed that patients with MSI-H levels have a better anti-tumor effect, the ability to inhibit tumor cell growth, and a better prognosis than those with MSI-L/MSS.[14]

MSI was first described in CRC. CRC can be divided into two, according to the different molecular mechanisms of MSI: CRC without a significant family genetic history and familial non-polyposis Lynch syndrome. Lynch syndrome is an autosomal dominant tumor syndrome caused by mutations in MMR strains, and 15% of CRC patients show DNA-MMR deficiency with MSI-H.[15] Most cases have MLH1 or MSH2 mutation or hypermethylation of the MLH1 promoter. Smyrk et al.[16] have shown that the tumors of people with MSI-H contain a high density of tumor-infiltrating lymphocytes, consisting of cytotoxic T lymphocytes, which can generate a specific anti-tumor immune response. Kim et al.[17] reported that patients with stage 1–3 MSI-H CRC

had a better clinical prognosis. Still, local recurrence and peritoneal metastasis were more common in these patients. Colon cancers with microsatellite instability show different clinical and pathological features. MSI is detected in more than 90% of patients with Hereditary Non-Polyposis Colorectal Cancer (HNPCC) and approximately 15% of sporadic colorectal cancers. Because sporadic colorectal cancers are much more common than hereditary forms, most tumors showing microsatellite instability are sporadic tumors.[18]

High-level microsatellite unstable (MSI-H) cancers are mostly located in the proximal colon. In 2/3 of HNPCC patients and more than 90% of patients with MSI-H sporadic colorectal cancer, the lesion is detected proximal to the splenic flexure.[19]

Although three methodologies have been utilized to determine MSI status: immunohistochemistry (IHC), polymerase chain reaction (PCR), and next-generation sequencing (NGS), due to their limitations, a non-invasive alternative is an unmet need. The heterogeneity of MSI-H status, poor DNA quality of biopsy samples, the invasive procedure, and the long duration period in their clinical application can be elaborated as downsides.[20,21] At this stage, FDG PET/CT may be positioned as a valuable molecular imaging modality that is less invasive.[22] Chung et al.[23] published that MSI status correlated with 18F-FDG uptake in gastric cancer.

Song et al.[9] used 18F-FDG PET/CT and demonstrated the relationship between MSI status and MTV in colorectal cancer. Their hypothesis that 18F-FDG PET/CT might be a helpful tool for noninvasively inferring MSI-H CRC patients was supported by their outcomes and confirmed with the results of Liu et al.[24] The 18F-FDG PET/CT reflected anatomic morphology and glucose metabolism, which contained lots of information about prognosis and treatment response. However, against these encouraging data, one should keep in mind that 18F-FDG PET/CT may have good prediction performance, but it cannot replace pathologic testing for examining MSI status.[25]

Jiang et al.[26] retrospectively analyzed the pretreatment parameters of PET and reported the highest diagnostic performance of MTV 3.0 and TLG 3.0 in predicting PD-L1 expression levels in CRC. Wu et al.[27] found that the quantitative imaging features derived from dual-energy computed tomography (DECT) achieved good predictive performance for MSI status in CRC patients. In addition, radiomics-based artificial intelligence, such as MRI-based deep learning models, also demonstrated optimal diagnostic capability for discriminating MSI from microsatellite stability. Wu et al.[27] stated that MTV with the percentage thresholds, rather than the fixed thresholds, showed better predictive performances of MSI. Liu et al.[24] reported that the metabolic parameters derived from 18F-FDG PET/CT could preoperatively predict the MSI status in CRC, with MTV 50% demonstrating the highest predictive performance and recommended using these parameters, the noninvasive evaluation of MSI can be achieved, and leverage immunotherapy in CRC patients.

In our study, we could not detect a significant difference in FDG uptake (SUVmax, SUVmean, MTV, and TLG) values between the microsatellite instability positive and microsatellite instability negative groups. Our findings do not fully coincide with the literature due to the small number of operabl CRC . Studies with larger series may provide a better understanding of the relationships between MSI status and FDG uptake values.

CONCLUSION

With the advancement of image analysis technology, MTV, and TLG, volumetric indexes derived from 18F-FDG PET have been proposed for risk stratification of cancer patients. Regarding the outcomes of this research, the semiquantitative and metabolic parameters obtained by PET/CT are not different in colorectal cancer cases with instable and stable microsatellites.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Dicle Universty Medical Faculty Ethics Committee for Non-interventional Studies (Date: 20.12.2023, Decision No: 10).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Data Availability
The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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